

WHAT IS CLAIMED IS:

1. A method of screening a candidate compound for use in inhibiting cellular proliferation, said method comprising the steps of:

5       expressing in a cell an antisense nucleic acid against a nucleic acid encoding a proliferation-required gene product so as to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

      contacting said sensitized cell with a candidate compound, wherein said candidate compound is not previously known to possess the ability to reduce cell proliferation;

10       determining whether said candidate compound inhibits the proliferation of said sensitized cell to a greater extent than said candidate compound inhibits the proliferation of a cell that is less sensitized than said sensitized cell.

2. The method of Claim 1, wherein said antisense nucleic acid is transcribed from an inducible promoter.

15       3. The method of Claim 2, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sub-lethal level.

4. The method of Claim 3, wherein said sub-lethal concentration of said inducer is such that growth inhibition is at least about 5% or more.

20       5. The method of Claim 1, wherein said gene product is a polypeptide.

6. The method of Claim 1, wherein said gene product is an RNA.

7. The method of Claim 1, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

8. The method of Claim 1, wherein said cell is from an organism selected  
25       from the group consisting of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Helicobacter pylori*, *Neisseria gonorrhoeae*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhimurium*, *Saccharomyces cerevisiae*, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella choleraesuis*,  
30       *Staphylococcus epidermidis*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Treponema pallidum*, *Bacillus anthracis*, *Yersinia pestis*, *Clostridium*

*botulinum*, *Campylobacter jejuni*, *Chlamydia trachomatis* and *Chlamydia pneumoniae* or any species falling within the genera of any of the above species.

9. The method of Claim 1, wherein said cell is an *E. coli* cell.

10. The method of Claim 1, wherein said candidate compound is a natural product.

11. A method of screening a candidate compound for use in inhibiting proliferation of a microorganism, said method comprising:

(a) identifying a gene or gene product required for proliferation in a first microorganism;

(b) identifying a homolog of said gene or gene product in a second microorganism;

(c) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said second microorganism;

(d) contacting said second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid, thus sensitizing said second microorganism;

(e) contacting the sensitized microorganism of step (d) with a candidate compound; and

(f) determining whether said candidate compound inhibits the proliferation of said sensitized microorganism to a greater extent than said candidate compound inhibits the proliferation of a microorganism that is less sensitized than said sensitized microorganism.

12. The method of Claim 11, wherein said step of identifying a gene involved in proliferation in a first microorganism comprises:

introducing a nucleic acid comprising a random genomic fragment from said first microorganism operably linked to a promoter wherein said random genomic fragment is in the antisense orientation; and

comparing the proliferation of said first microorganism transcribing a first level of said random genomic fragment to the proliferation of said first microorganism transcribing a lower level of said random genomic fragment, wherein a difference in proliferation indicates that said random genomic fragment comprises a gene involved in proliferation.

13. The method of Claim 11, wherein said step of identifying a homolog of said gene in a second microorganism comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a database using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters.

14. The method of Claim 11, wherein said step of identifying a homolog of said gene in a second microorganism comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene.

15. The method of Claim 11, wherein the step of identifying a homolog of said gene in a second microorganism comprises expressing a nucleic acid which inhibits the proliferation of said first microorganism in said second microorganism.

16. The method of Claim 11, wherein said inhibitory nucleic acid is an antisense nucleic acid.

17. The method of Claim 11, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.

18. The method of Claim 11, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.

19. The method of Claim 11, wherein the step of contacting the second microorganism with a proliferation-inhibiting amount of said nucleic acid sequence comprises directly contacting said second microorganism with said nucleic acid.

20. The method of Claim 11, wherein the step of contacting the second microorganism with a proliferation-inhibiting amount of said nucleic acid sequence comprises expressing an antisense nucleic acid to said homolog in said second microorganism.

21. The method of Claim 11, wherein said candidate compound is a natural product.

22. A method of screening a candidate compound for use in inhibiting proliferation, said method comprising:

(a) identifying an inhibitory nucleic acid sequence which inhibits the activity of a gene or gene product required for proliferation in a first microorganism;

(b) contacting a second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid, thus sensitizing said second microorganism;

5 (c) contacting the proliferation-inhibited microorganism of step (b) with a candidate compound; and

(d) determining whether said candidate compound inhibits the proliferation of said sensitized microorganism to a greater extent than said candidate compound inhibits the proliferation of a microorganism that is less sensitized than said sensitized microorganism.

10 23. The method of Claim 22, wherein said inhibitory nucleic acid is an antisense nucleic acid which inhibits the proliferation of said first microorganism.

24. The method of Claim 22, wherein said inhibitory nucleic acid comprises a portion of an antisense nucleic acid which inhibits the proliferation of said first microorganism.

15 25. The method of Claim 22, wherein said inhibitory nucleic acid comprises an antisense molecule against the entire coding region of the gene involved in proliferation of the first microorganism.

20 26. The method of Claim 22, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding the gene involved in proliferation of the first microorganism.

27. The method of Claim 22, wherein said candidate compound is a natural product.

28. A method of screening a candidate compound for use in inhibiting cellular proliferation, said method comprising:

25 contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell;

contacting said cell with a candidate compound, wherein said candidate compound is not previously known to possess the ability to reduce cell proliferation; and

30 determining whether said candidate compound reduces proliferation to a greater extent than said candidate compound reduces proliferation of a cell which has not been contacted with said agent; and

determining whether said candidate compound inhibits the proliferation of said sensitized cell to a greater extent than said candidate compound inhibits the proliferation of a cell that is less sensitized than said sensitized cell.

5        29.     The method of Claim 28, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.

30.     The method of Claim 28, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antibiotic.

10       31.     The method of Claim 28, wherein said cell contains a temperature sensitive mutation which reduces the activity or level of said gene product required for proliferation of said cell.

32.     The method of Claim 28, wherein said candidate compound is a natural product.

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